REMARKS

Claims 20-35 were pending in the application. Claims 27-30 and 34-35 are canceled without prejudice as being directed to a non-elected invention. Claims 21-23 were also cancelled without prejudice in view of the amendment to claim 20. New claims 36-51 have been added. Thus, claims 20, 24-27, 31-33, and 36-51 are now pending.

Claims 26 and 31-32 have been amended to correct for dependencies and informalities. Support for amended claim 20 can be found in the claims as originally filed and throughout the specification, including at least at page 10, lines 3-6 and lines 10-15. Support for new claim 36 can be found in the specification at least at page 10, lines 10-11. Support for new claims 37 and 46 can be found throughout the specification, at least at page 12, lines 21-22 and 25-30 . Support for new claims 38 and 47 can be found throughout the specification, at least at page 12, lines 32-33. Support for new claims 39 and 48 can be found throughout the specification, at least at page 12, lines 16-20 and 31-32. Support for new claims 40 and 49 can be found throughout the specification and in the claims as originally filed. Support for new claims 41 and 50 can be found throughout the specification, at least at page 13, lines 10-14. Support for new claims 42 and 51 can be found throughout the specification, at least at page 13, lines 10-11. Support for new claims 43-44 can be found throughout the specification, at least at page 9, lines 25-27. Additional support for new claim 43 can be at page 9, lines 25-27. Additional support for new claim 45 can be found at page 10, lines 1-2. No new matter has been added.

Amendments to and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 20-27 and 31-33 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 20-27 and 31-33 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one of ordinary skill in the art to make or use the claimed invention. The Examiner states that "[n]either the specification nor any prior art teaches that reduced lymph node weight in the model mice used is indicative of tumor reduction." The Examiner also rejects claims 20-27 and 31-33 for recitation of the phrase "effective amount," stating that, "the specification does not teach what is an effective amount of a soluble LT beta receptor." Applicants respectfully traverse this rejection.

As amended, claim 20 relates to methods for treating follicular lymphoma in a subject comprising administering an amount of a composition comprising a soluble lymphotoxin-beta receptor (LT beta-R) and a pharmaceutically acceptable carrier, such that treatment occurs. In one embodiment, the treatment is tumor regression or arrest. The claimed invention also includes a method for disrupting interaction of a B cell lymphoma with its environment in a subject, comprising administering to the subject a composition comprising a soluble LT-beta-R and a pharmaceutically acceptable carrier, such that disruption of the interaction of the B cell lymphoma with its environment occurs. In one embodiment, the soluble lymphotoxin-beta receptor comprises a ligand binding domain that can selectively bind to a surface LT ligand. In another embodiment, the soluble LT-beta-R comprises a soluble LT-beta-R fused to one or more heterologous protein domains.

While the Examiner acknowledges that the "chimeric soluble receptor used for the Experiment 1 and Table 1...reduces lymph node weight," the Examiner is of the opinion that "[d]emonstration [of] the smaller LN weight cannot alone support the predictability of the method," where in the method is cancer treatment. Applicants respectfully traverse this statement on the grounds that the specification teaches one of ordinary skill in the art how to treat follicular lymphoma by administration of a composition comprising a soluble lymphotoxin-beta receptor (LT beta-R) and a pharmaceutically acceptable carrier. Applicants teach that

disruption of the LT pathway using LTBR inhibitors disrupts the interaction between follicular lymphomas and the follicular dendritic cells (FDC), which in turn leads to slowed or arrested growth of tumors. Applicants provide a working example which illustrates that administration of a LTBR blocking agent, *e.g.*, an LTBR-hIgG1 fusion protein, reduces tumor size in an appropriate animal model. Specifically, the working example demonstrates that administration of an LTBR-hIgG1 fusion protein reduces lymph node size in SJL mice with transplanted tumors consisting of RCS cells (see page 11, lines 9-19 of specification). Thus, Applicants' working example demonstrates a reduction in the lymph node tumor in a murine cancer model for follicular lymphoma following administration of an LTBR inhibitor.

Applicants submit that the Examiner has not cited any objective evidence in support of his position that one of ordinary skill in the art would find the claimed invention, namely treating follicular lymphoma with a soluble LTBR, unpredictable, and, furthermore, would not reasonably extrapolate from successful reduction in tumor weight in an appropriate animal model in treating cancer. Despite this lack of evidence by the Examiner, Applicants provide objective evidence in support of our position that a reduction in tumor weight in an animal model is a useful prediction of efficacy in reducing or arresting tumor growth in humans. Applicants submit the following references for consideration by the Examiner.

Korkut et al. (1991) *PNAS* 88:844-848 (attached herewith as Appendix A; hereinafter "Korkut") provides a comparative study of the effects of two drugs, *i.e.*, [D-Trp^6] LH-RH and SB-75, for the treatment of prostrate cancer using the R-3327 Dunning rat adenocarcinoma model. As shown in Table 2 at page 846, Korkut uses tumor weight to study the drugs efficacy in comparison with a nontreated control group, as described in the results at page 846, column 1. The authors conclude that the results, including the reduction in tumor weight, "suggest its [SB-64] possible usefulness for the treatment of hormone-sensitive tumors" (see last sentence of abstract, page 844).

Shirasaka *et al.* (1996) *Cancer Research* 56:2602-2606 (attached herewith as Appendix B; hereinafter "Shirasaka") teach the antitumor activity of two drugs, S-1 and UFT. Shirasaka

uses a rat model for human colon carcinoma, wherein tumor cells from the KM12C cell line are injected into the colonic wall of the rat. Shirasaka describes various assays, including measurement of the tumor weight with and without treatment, in order to evaluate "anticancer agents against colorectal cancer and to evaluate practically the antitumor activity of...S-1...and UFT" (see first sentence, abstract at page 2602). As shown in Table 1 at page 2604, the authors calculated the tumor weight of the S-1 and UFT treated rat compared to the untreated rats to determine the efficacy of S-1 and UFT in the reduction of the injected tumor. Based on the data described in Table 1, the authors conclude at page 2603, 2nd column that UFT was not as effective at "suppress[ing] tumor growth" as S-1.

Halmos and Schally (1997) *PNAS* 94:956-960 (attached herewith as Appendix C; hereinafter "Halmos") describes studies which evaluate the efficacy of RC-3095 (an antagonist of bombesin/gastrin-releasing peptide (BN/GRP)) for the treatment of small-cell lung carcinoma (SCLC). The Halmos study describes treatment of mice with xenografts of human cancer cell lines, i.e., the H-128 SCLC cell line. As described at page 957, 1st column, mice were injected with tumor cells to promote tumor growth. Tumors were allowed to grow for seven weeks, at which point the tumors were dissected out, minced, and transplanted into the experimental mice. Tumors were allowed to grow for two weeks in the transplanted mice prior to the administration of RC-3095 or a saline control for four weeks. Tumor volume was assayed during the four week treatment period, and tumor weight was determined at the end of the study following anaesthetization of the animals. As shown in Table 1 at page 957, tumor weight was reduced in the experimental RC-3095 animals compared to the controls. Based on the results, the authors conclude that, "[t]he present study demonstrates that the potent BN/GRP anatagonist RC-3095 significantly inhibits the growth of human SCLC H-128 cell line xenografted into nude mice" (see page 958, 2nd column).

Finally, Inoue *et al.* (2000) *Clinical Cancer Research* 6:4874-4884 (attached herewith as Appendix D; hereinafter "Inoue") describe the efficacy of paclitaxel and antibody C225 in a mouse model for bladder cancer, specifically transitional cell carcinoma (TCC) of the bladder.

As described at page 4875, 2nd column, the bladder walls of mice were injected with tumor cells (253J-BV) to initiate tumor growth. As shown in Table 1 at page 4877, mice treated with paclitaxel, C225 of a combination of the two showed a decrease in tumor weight in comparison to the control mice. Based on these data, the authors conclude at page 4880, second column, that the combination treatment of paclitaxel and C225 was "significantly more effective at eradicating bladder tumors than with C225 alone." The authors summarize the findings of the study by stating that, "[t]hese studies indicate that therapy with paclitaxel increases the ability of C225 to inhibit tumorigenicity" (see page 4874, abstract). Applicants also point out that following these experiments, C225 (also known as Cetuximab by Imclone) was advanced in development as a cancer therapy and is currently entering a Phase III clinical study (see www.Cetuximab.com).

Applicants present the above-mentioned references as evidence of the known correlation between reduction in tumor weight in an appropriate animal model and predictability in treating cancer. Accordingly, it is Applicants' position that one of ordinary skill in the art can extrapolate from the entire teachings of Applicants, including reduction in tumor weight in an animal model to predictability in treating follicular lymphoma in humans. In contrast to the Examiner's assertion, the enclosed references (Appendices A-D) also teach that reduced tumor weight in an animal model is indicative of tumor reduction. Thus, the teachings of the specification as a whole, enable one of ordinary skill in the art to make and use the claimed invention.

The Examiner states that the specification fails to teach "(1) if the mice that received control developed tumor in the lymph node samples; (2) whether the reduced lymph node weight of the mice received the chimeric protein is a result of shrinkage of lymph nodes due to absence of LT-beta-R signaling; (3) any evidence the reduced lymph node weight is [an] indication of reduction of tumor."

Regarding point (1), Applicants direct the Examiner to Table 1 at page 11 of the specification which provides both control and experimental data described in Example 1. For example, Experiment 3 of Table 1 provides results from an experiment wherein the lymph node

(LN) size in control mice who received the tumor transplant and a control injection of huIgG is compared to the LN size of experimental mice who received the tumor transplant and also received a single or multiple dose of mLTβR-Ig. The average LN weight of the control mice in Experiment 3 was 2.34, while the experimental mice had a calculated LN average weight of 1.1 and 0.78, respectively. Thus, the experimental animals showed a 52% and 67% decrease in LN weight, *i.e.*, tumor weight.

As described in Example 1, Applicants demonstrate that mice who normally would develop tumors (as evidenced by the control mice who developed tumors and by the established SJL/RCS animal model system) developed tumors of a reduced weight because the mice were given doses of the LTβR-hIgG1 fusion protein. As described in footnote "a" to Table 1 (see page 12, line 5 of the specification), the lymph node weights described are given as a percent of the total body weight. Applicants teach that a typical LN weight is 0.5% of the total body weight. As shown in Table 1, all of the lymph nodes in the treated and untreated controls were well above the usual 0.5% LN weight, indicating that tumors were present. Mice that received an LT-beta-R signaling inhibitor showed a reduction in the tumor size. Thus, Applicants demonstrate that tumor size is reduced in treated animals.

With regard to points (2) and (3), Applicants submit that treatment with the soluble LTβR-hIgG1 fusion protein, as described in Example 1 of the specification, causes a reduction in lymph node tumor weight as a result of a disruption between the tumor and its environment and an inhibition of LT-beta-R signaling. Lymph node development has been shown to depend on the LT pathway (see Rennert *et al.* (1996) *J Exp Med* 184:1999-2006 described at page 2, lines 22-27 of the specification), wherein the lymph nodes were disrupted in mice who were administered an LTβR-Ig fusion during embryogenesis. Applicant's experiment was performed in adult mice, whose lymph nodes were presumably already developed. Therefore, the inhibition of LT-beta-R signaling would not impede the development of the LN, but rather was shown to affect tumors growing in the LN environment.

The Examiner states that the specification does not teach one of ordinary skill in the art what an "effective amount" is. Applicants have amended the claims to delete reference to the term "effective amount," The amended claims are directed to a method of treating follicular lymphoma comprising administering an effective amount of a composition comprising a soluble lymphotoxin-beta receptor (LT beta-R) and a pharmaceutically acceptable carrier, such that treatment occurs. Applicants maintain, however, for the reasons already made of record as well as those set forth below with respect to the 112 2nd paragraph rejection, that the specification fully enables one of ordinary skill in the art to determine an "effective amount" of the claimed composition for a method of treating follicular lymphoma.

In view of the above, Applicants maintain that the specification fully enables one of ordinary skill in the art to make and use the claimed invention, and respectfully request that the Examiner withdraw the 112, first paragraph rejection

II. Rejection of Claims 20-27 and 31-33 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 20-27 and 31-33 under 35 U.S.C. § 112, second paragraph for use of the term "effective amount" which the Examiner asserts is not clearly defined in the specification. Claim 20 has been amended to specify a method for treating follicular lymphoma in a subject comprising administering an amount of a composition comprising a soluble lymphotoxin-beta receptor (LT-beta-R) and a pharmaceutically acceptable carrier, such that treatment occurs. In view of the amendment to claim 20, Applicants submit that the rejection is rendered moot.

Applicants maintain, however, that the metes and bounds of an "effective amount" is clearly defined. Applicants submit that recitation of the term "effective amount" is art-recognized and is intended to mean an amount sufficient to effect beneficial or desired results as set forth in Applicants' claims, for example, such as treating follicular lymphoma, wherein the effective amount results in tumor regression or arrest. As described in the specification at page 10, lines 3-5, Applicants teach that an effective amount of a composition which treats subjects

having tumors or lymphomas, is the amount that inhibits the LT pathway. As described in the specification at page 10, lines 13-15, one of ordinary skill in the art would recognize when tumor regression or arrest has occurred using methods known in the art, and thus would recognize an "effective amount" of the composition to be used.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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